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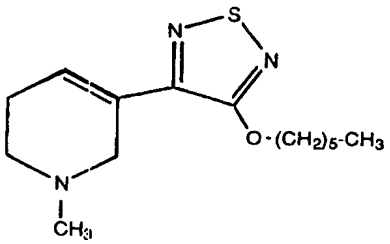
(54) Title: METHOD FOR TREATING DEMENTIA DUE TO AIDS



(I)

(57) Abstract

The present invention provides a method for treating Dementia Due to HIV Disease using a compound of the Formula (I).

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METHOD FOR TREATING DEMENTIA DUE TO AIDS

This invention provides a method for treating or alleviating the symptoms of dementia due to AIDS, comprising administering an effective amount of 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine.

Human immunodeficiency virus (HIV) disease may often result in the patient being further incapacitated due to the serious psychological disorder, Dementia Due to HIV Disease (characterized in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (American Psychiatric Association, 1994) DSM-IV as catagory 294.9). Such Dementia can result in hospitalization of the patient, stress for caretakers, and increased medical expense.

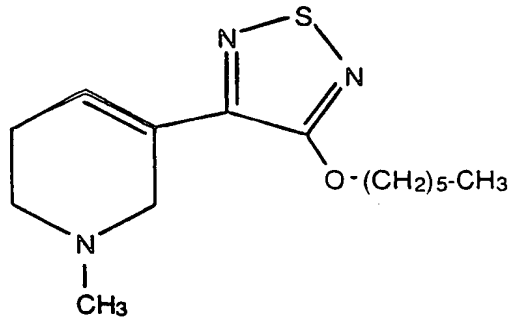
Sauerberg *et al.* in U.S. Patent 5,043,345 ('345) disclose the 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine compound which Applicants have discovered is useful for treating Dementia due to HIV Disease. The compounds in the '345 patent are taught to be useful in treating Alzheimer's disease, severe painful conditions, and glaucoma. There is no disclosure in the patent of using the compounds to treat Dementia due to HIV Disease.

Surprisingly, we have discovered that 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine, thought to be a muscarinic agonist, can be useful for treating Dementia Due to HIV Disease. The present invention relates to a method of treating Dementia Due to HIV Disease. More specifically, the invention provides a method of treating Dementia Due to HIV Disease in humans using 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine.

As noted hereinbefore, the compounds employed in the method of the present invention are known. Methods of preparing the compounds, as well as pharmaceutical

formulations containing the compounds, are taught by Sauerberg in U.S. Pat. No. 5,043,345 herein incorporated by reference.

The present invention provides a method for treating Dementia Due to HIV Disease in humans comprising administering to a human in need thereof, an effective amount of a compound of Formula I:



I

or

a pharmaceutically acceptable salt or solvate thereof.

It is to be understood that the invention extends to the use of each of the stereoisomeric forms of the compound of the present invention as well as any pure diastereomeric, pure enantiomeric, and racemic forms of the named compounds.

The term "effective amount", as used herein, represents an amount of compound necessary to prevent or treat a human susceptible to or suffering from Dementia due to HIV Disease following administration to such human. The active compound is effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.005 to about 500 mg/kg of body weight. In the treatment of adult humans, the range of about 0.05 to about 100 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances

including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compound may be administered orally to humans susceptible to or suffering from Dementia Due to HIV Disease, the compound is particularly well suited to be administered transdermally. When the compound is delivered transdermally, it is preferred that the effective amount is from about 50mg to about 100mg per day delivery of base compound. It is especially preferred that such patch delivers an effective amount for about three to seven days.

The compound may further be delivered by a variety of other pharmaceutically accepted routes including, but in no way limited to parenterally, subcutaneous, intranasal, intramuscular and intravenous routes. Such formulations may be designed to provide delayed or controlled release using formulation techniques which are known in the art.

As used herein the term "treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed physical and/or mental condition once it has been established or alleviation of the characteristic symptoms of such condition.

As used herein the term "Dementia Due to HIV Disease" refers to a disorder that upon neuropathological examination may commonly involve diffuse multifocal destruction of the white matter and subcortical structures. The spinal fluid may show normal or slightly elevated protein and a mild lymphocytosis, and HIV can usually be isolated directly from the cerebrospinal fluid. Dementia associated with HIV is typically characterized by slowness, poor concentration, difficulties with problem solving, and forgetfulness. Behavioral manifestations most commonly include apathy and social withdrawal, and occasionally these may be accompanied by delirium, delusions, or

hallucinations. Tremor, impaired rapid repetitive movements, imbalance, ataxia, hypertonia, generalized hyperreflexia, positive frontal release signs, and impaired pursuit and saccadic eye movements may be presented on physical examination.

Dementia Due to HIV Disease has been characterized in the DSM-IV-R. Diagnostic and Statistical Manual of Mental Disorders, Revised, 4th Ed. (1994). The DSM-IV-R was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic catagories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

The compounds employed in the invention are not believed to act via the GABA/benzodiazepine, 5HT1A, or D1 receptor systems in humans. Rather, the activity of the present compound as a treatment for Dementia Due to HIV Disease is believed to be based upon modulation of muscarinic cholinergic receptors. However, the mechanism by which the present compounds function is not necessarily the mechanism stated *supra.*, and the present invention is not limited by any mode of operation.

The following Examples are studies to establish the usefulness of the named compounds for treating Dementia Due to HIV Disease.

Example 1

Human Clinical Trials

Finally, the activity of 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine for treating or alleviating Dementia Due to HIV Disease can be demonstrated by human clinical trials. The study was designed as a double-blind, parallel, placebo-controlled multicenter trial. The patients were randomized into four groups, placebo and 25, 50, and 75 mg tid of test compound.

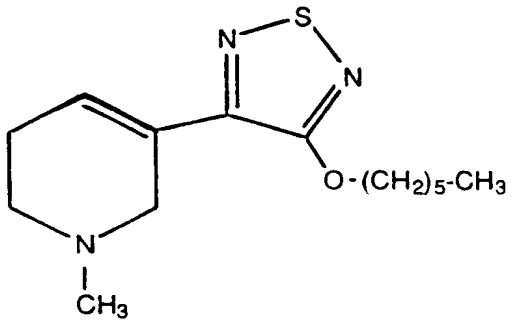
The dosages were administered orally with food. Patients were observed at four visits to provide baseline measurements. Visits 5-33 served as the treatment phase for the study.

During the visits, patients and their caregivers are questioned and observed for signs of agitation, mood swings, tremor, delirium, social withdrawal, and concentration abilities. Each of these behaviors are indicative of the effect of the test compound on Dementia Due to HIV Disease. Additionally, patients are asked a series of questions designed to assess ability to solve problems and slowness.

Treatment groups are compared with respect to the number and percent of patients who ever had the symptom during the double-blind portion of the study (visits 5 through 33), at a severity that was worse than during the baseline visits (1 through 4).

Claims

1. A method for treating Dementia Due to HIV Disease in humans comprising administering to a human in need thereof, an effective amount of a compound of Formula I:



a pharmaceutically acceptable salt thereof.

2. A method of **Claim 1** wherein the effective amount is from 1 mg/kg to about 100 mg/kg per day.

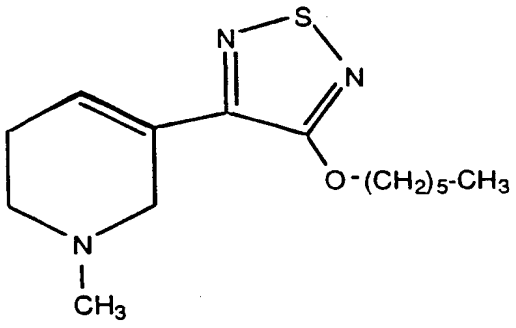
3. A method of **Claim 2** wherein the effective amount is from about 50 mg/kg to about 100 mg/kg per day.

4. A method of **Claim 1** wherein the effective amount is delivered using a transdermal patch.

5. A method of **Claim 4** wherein the transdermal patch delivers from about 50 to about 100 mg of base compound per day.

6. A method of **Claim 5** wherein the transdermal patch delivers an effective amount for three (3) to seven (7) days.

7. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for use in the treatment of Dementia Due to HIV Disease.

8.A compound of Claim 7 wherein the compound is administered using a transdermal delivery formulation.

9. A compound of Claim 7 wherein the compound is administered using a transdermal delivery system that delivers and effective amount of compound from about three (3) to about seven (7) days.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19184

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61F 13/00; C07D 417/04
US CL : 424/449; 514/342
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/449; 514/342

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS
search terms: tetrahydropyridine, piperidine, dementia, Alzheimer's, HIV, AIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,043,345 A (SAUERBERG et al.) 27 August 1991, see entire document.	7-9 --- 1-6
Y	US 4,826,843 A (MATTSON et al.) 02 May 1989, column 3, lines 9-30 and column 10, lines 18-28.	1-9
Y	US 5,232,929 A (DESAI et al.) 03 August 1993, column 4, line 49 through column 5, line 10; column 8, lines 63-65.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Form PCT/ISA/210 (second sheet)(July 1992)*

(group 1) or 1 g calcium daily plus 400 mg etidronate (group 2) for 2 weeks out of 15. BMD of L1–L4 vertebrae and neck of femur was measured by Lunar DPX dual X-ray absorptiometry at baseline (year 0) and annually.

Changes in mean BMD based on actual and percentage values were analysed with paired *t* tests. Comparisons between groups were made with independent *t* tests.

Differences in age, sex, and steroid dose between groups were not statistically different:

	Year 0–1		Year 0–2	
	Group 1	Group 2	Group 1	Group 2
Number	18	20	12	9
Mean age	64	65	69	66
Mean daily steroids	8·9 mg	8·4 mg	6·9 mg	6·6 mg

Etidronate was well tolerated and taken at different times of the day from calcium. Some patients were withdrawn, mainly due to reduction of steroid therapy to less than 5 mg daily. Mean spinal BMD in the etidronate group rose by 4·1% after 1 year ($p<0·01$) and by 4·8% after 2 years ($p<0·05$). Mean spinal BMD of the calcium alone group decreased from baseline by 0·8% at year one ($p=0·429$) and by 0·7% ($p=0·612$) at year two. Most patients who took etidronate showed an increase in BMD, whereas most on calcium alone showed a decrease. A comparison of the spinal changes between the groups was significant at year one ($p<0·01$) and year 2 ($p<0·05$).

In the hip, none of the changes was statistically significant. Both groups showed a decrease of about 1% between baseline and year one. The etidronate group showed an increase of 3% after two years which was not significant.

Cyclical etidronate given at the beginning of steroid treatment has been reported to inhibit bone loss.[1] We conclude that cyclical etidronate increases lumbar spine BMD in patients receiving steroids in the first 2 years of treatment but we can show no clear effect on femoral BMD. Early use of cyclical etidronate in patients likely to remain on steroids for long periods may reduce bone morbidity but longer studies monitoring fracture rate are needed.

Tacrine for senile dementia of Alzheimer's or Lewy body type

SIR—In an earlier report in this journal Levy and colleagues[1] described their findings in 3 subjects treated with tacrine for presumed Alzheimer's disease, but in whom the necropsy diagnosis confirmed mixed Alzheimer's and Lewy body pathology. That these 3 subjects had Lewy bodies and were responders has raised the suggestion that tacrine may be mainly of benefit in this type of dementia, rather than in Alzheimer's disease alone. We report our findings in 10 subjects who received tacrine and later underwent necropsy.

9 of these patients were recruited into our main study of tacrine, 2 of whom had similar pathological changes to the 3 cases described by Levy et al. Of these 2, 1 with a clinical presentation indistinguishable from Alzheimer's disease was withdrawn after 4 weeks because of hepatotoxicity. The other initially presented as Alzheimer's disease but after 12 months developed other symptoms including extrapyramidal features, indicating the need to change the diagnosis. This latter case, together with 3 others with a typical clinical presentation of Alzheimer's disease confirmed at neuropathological examination, responded in terms of improvement or stabilisation in cognitive ability and activities of daily living score. A further case, again clinically and neuropathologically diagnosed as Alzheimer's disease, responded initially but this response was not sustained. Each of these subjects deteriorated during the placebo period. The remaining subjects, and in addition 1 other who was treated for 12 months in an open study, failed to respond and had neuropathologically confirmed Alzheimer's disease.

It is clear from our findings that the response to tacrine is not confined to those subjects whose brains contain Lewy bodies. It is, however, probable that both Alzheimer and Lewy body pathology each contribute to the cholinergic decline, with lower concentrations of cholinergic markers in cases where both pathologies are present. Such cases may benefit most from anticholinesterase treatments because, for a given level of dementia, a neurochemical treatment is likely, within certain limits, to provide greater benefit to those with the greater neurochemical lesion. This hypothesis remains to be confirmed.

G K Wilcock, M I Scott
Department of Care of the Elderly, Frenchay Hospital, Bristol BS16 1LE, UK.

1 Levy R, Eagger S, Griffiths M, et al. Lewy bodies and response to tacrine in Alzheimer's disease. *Lancet* 1994; **343**: 176.

HIV and lesbian sex

SIR—Raiteri and colleagues report (July 23, p 270) a study of 18 couples to assess the risk of HIV-1 transmission through lesbian sex. The 18 couples were in steady relationships; 1 was HIV-1 positive, the other was not. The couples kept a 3-month record of sexual activity and were followed up for 6 months thereafter to detect any HIV-1 seroconversion. Raiteri et al assess which of the self-declared sexual practices carried a high risk of transmission, and highlighted those factors. At the end of the study, there was no evidence of HIV-1 transmission from the seropositive woman to her partner. Although qualifying the conclusion with a call for further studies "to confirm these results", Raiteri et al state that their findings "support a non-existent risk of viral transmission in HIV-1 discordant lesbian couples engaging in sex acts that have a theoretically high transmission risk."

Leaving aside the question of whether there would be general agreement of the sexual-practice risk ratings assigned by Raiteri et al, let us suppose that the "true 3-month risk" of HIV-1 transmission in the couples was as high as 5% (1 in 20). The probability of such a couple avoiding transmission over 3 months is 0·95. The probability of 2 such couples avoiding transmission is $0·95^2$ (0·9025), and that of observing 18 similar couples who avoid transmission is $0·95^{18}$ (or 0·3972). In other words, at this quite high level of postulated risk, there is a nearly 40% probability by chance alone of finding no transmission in the study described by Raiteri and colleagues. Indeed, the 3-month risk needs to be as high as 15·4% (nearly 1 in 6) before the random probability of finding no transmission in this study falls below the conventional significance level of 0·5.